

Bioactive Compounds in Herbal Remedies: Friend or Foe in Hepatic and Renal Health?

Mugisha Emmanuel K.

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

Herbal remedies have been used for centuries in various cultures for the treatment of diseases, with bioactive compounds as their core therapeutic agents. These compounds, including flavonoids, alkaloids, glycosides, and saponins, are known to possess potent antioxidant, anti-inflammatory, and hepatoprotective properties. However, there is an increasing concern about their safety, especially concerning their effects on liver and kidney health. While certain bioactive compounds can provide therapeutic benefits, they may also induce hepatotoxicity and nephrotoxicity when used improperly or over long durations. This review critically examines both the positive and negative impacts of bioactive compounds in herbal remedies on hepatic and renal health, focusing on mechanisms of action, histopathological evidence, and risk factors influencing toxicity. The review highlights the need for more rigorous safety assessments, standardization of herbal products, and consideration of individual patient factors, such as pre-existing liver or kidney conditions. It also calls for the establishment of regulatory frameworks for herbal medicine to ensure their safety in clinical practice.

Keywords: Bioactive compounds; Herbal remedies; Hepatotoxicity; Nephrotoxicity; Liver and kidney health

INTRODUCTION

Herbal remedies have been used for thousands of years in various cultures around the world, with a significant focus on the healing properties of plants [1]. These remedies have remained a cornerstone in traditional medicine due to their diverse range of therapeutic benefits. Central to these remedies are bioactive compounds, which are responsible for the medicinal properties of plants. Bioactive compounds exhibit a variety of biological activities, such as antioxidant, anti-inflammatory, antimicrobial, anticancer, and analgesic effects, which contribute to their widespread use in the treatment of many diseases [2]. Common bioactive compounds include flavonoids, alkaloids, glycosides, tannins, and terpenoids, all of which are believed to alleviate symptoms, improve physiological functions, and even cure certain diseases by targeting specific molecular pathways within the body [3]. In recent decades, there has been a significant rise in the global use of herbal remedies [4]. This surge is primarily driven by the growing perception that herbal products are safe, effective, and easily accessible alternatives to conventional pharmaceuticals. With this increase in use, however, comes a growing concern regarding the safety profile of many herbal products, especially

regarding their potential hepatotoxicity and nephrotoxicity. The liver and kidneys are central organs in the detoxification process and play a crucial role in eliminating metabolic waste products from the body. As such, they are highly susceptible to damage from harmful compounds, including bioactive substances from herbal remedies [5,6]. While these bioactive compounds can provide a therapeutic benefit, their effects on the liver and kidneys can be detrimental, particularly when used improperly, in excess, or over prolonged periods. Although many of the compounds found in herbal remedies have been studied for their benefits, few have undergone rigorous testing for potential toxicity. As a result, this review will delve into the dual nature of bioactive compounds in herbal remedies, examining both their beneficial and harmful effects on hepatic and renal health [7]. The focus will be on understanding how these compounds may contribute to liver and kidney function when used correctly, and how improper use may lead to adverse effects. This review aims to provide a balanced perspective on the role of herbal remedies in modern healthcare, emphasizing the importance of understanding the potential risks associated with their use.

Beneficial Effects of Bioactive Compounds on Hepatic and Renal Health

Many bioactive compounds found in herbal remedies have been shown to possess both hepatoprotective (liver-protecting) and nephroprotective (kidney-protecting) properties. The liver and kidneys, both vital detoxifying organs, are often exposed to external toxins and endogenous metabolic waste products, making them vulnerable to damage [5]. Consequently, the role of herbal remedies in maintaining liver and kidney health is increasingly recognized, especially as adjuncts in the management of chronic conditions like diabetes, hypertension, and chronic kidney disease [6]. Silymarin, derived from *Silybum marianum* (milk thistle), is one of the most well-documented herbal compounds for its hepatoprotective effects. Studies have shown that silymarin works by stabilizing the membranes of hepatocytes (liver cells), scavenging free radicals, and enhancing the activity of detoxifying enzymes such as superoxide dismutase (SOD) and glutathione S-transferase [8]. These actions protect the liver from oxidative stress and inflammation, which are key factors in the development of liver damage caused by factors like alcohol consumption, viral infections, and exposure to environmental toxins. Additionally, silymarin has been shown to promote liver regeneration by stimulating the synthesis of proteins involved in cellular repair. Its ability to reduce liver fibrosis and cirrhosis in preclinical models makes it a valuable agent in the management of liver diseases [9].

Another prominent bioactive compound is curcumin, the active compound in *Curcuma longa* (turmeric). Curcumin is a potent anti-inflammatory and antioxidant agent that has demonstrated substantial therapeutic potential in both liver and kidney diseases [10]. In liver health, curcumin has been shown to reduce liver fibrosis and prevent hepatocellular injury by inhibiting pro-inflammatory cytokines like TNF- α and IL-6, and by scavenging free radicals that contribute to oxidative stress [11]. Curcumin also has the ability to modulate metabolic pathways involved in lipid metabolism, further enhancing its role as a hepatoprotective agent [12]. In kidney health, curcumin has demonstrated a protective effect against diabetic nephropathy by reducing inflammation and oxidative stress in renal tissues, thus improving kidney function in preclinical models [13]. In summary, bioactive compounds in herbal remedies offer valuable therapeutic benefits for hepatic and renal health. They work primarily through their antioxidant, anti-inflammatory, and detoxifying properties, which help protect these vital

organs from damage caused by oxidative stress and inflammatory processes. As research into these compounds continues, it is expected that they will play an increasingly important role in the treatment and prevention of liver and kidney diseases.

Hepatotoxicity and Nephrotoxicity Induced by Bioactive Compounds

While many bioactive compounds from herbal remedies provide therapeutic benefits, certain compounds, especially when consumed in excessive amounts or for prolonged periods, can result in hepatotoxicity (liver toxicity) and nephrotoxicity (kidney toxicity) [14]. These adverse effects are particularly concerning because the liver and kidneys play crucial roles in detoxifying harmful substances and maintaining metabolic balance.

Tannins, a class of polyphenolic compounds found in various herbs, such as *Camellia sinensis* (green tea) and *Vitis vinifera* (grape seed), have been associated with liver toxicity when consumed in excess [15]. Tannins can induce hepatocellular damage by promoting oxidative stress and inflammation in liver cells. This can lead to liver cell apoptosis (programmed cell death), fibrosis, and in some cases, cirrhosis [16]. While moderate consumption of green tea is generally considered safe, excessive intake, especially in the form of concentrated extracts, can overwhelm the liver's detoxification capacity, leading to harmful effects [17]. Tannins have been shown to increase lipid peroxidation in the liver, which damages cellular membranes and disrupts normal cellular functions [18]. In addition, tannins may also interfere with iron absorption, contributing to iron overload in the liver, a condition that can further damage liver tissues over time [19]. Similarly, pyrrolizidine alkaloids, which are naturally occurring compounds found in several plant species such as *Senecio vulgaris* (groundsel), *Crotalaria* species, and *Heliotropium* species, are well-known hepatotoxins [20]. These alkaloids can cause severe liver damage by inducing hepatocellular necrosis (cell death) and portal hypertension, which can progress to liver failure if not properly managed [20]. Pyrrolizidine alkaloids are metabolized in the liver to highly reactive metabolites that covalently bind to cellular macromolecules, disrupting normal liver function [21]. The resulting hepatic damage is often characterized by fibrosis, cirrhosis, and in some cases, hepatocellular carcinoma [22]. Due to these toxic effects, pyrrolizidine alkaloids have been banned or restricted in many countries. However, they still pose a risk in some traditional medicine practices where unregulated herbal formulations may contain these alkaloids.

Nephrotoxicity is also a significant concern with certain herbal compounds. One of the most notorious nephrotoxic compounds is aristolochic acid, found in species of *Aristolochia*, such as *Aristolochia clematitis* and *Aristolochia fangchi* [23,24,25]. Aristolochic acid has been strongly linked to acute kidney injury (AKI) and chronic kidney disease (CKD) [23]. It exerts its nephrotoxic effects by binding to DNA and forming adducts, which can lead to mutations, DNA damage, and cellular apoptosis [23]. In the kidneys, aristolochic acid causes renal tubulointerstitial fibrosis and glomerular damage, which may result in irreversible kidney damage and eventual renal failure [24]. The use of aristolochic acid-containing herbs has led to significant health issues worldwide, including cases of kidney failure and cancer [24]. Despite its nephrotoxic effects being well-documented, aristolochic acid continues to be found in some traditional herbal preparations, particularly in some regions of Asia and Africa, where it is used for weight loss and detoxification [25]. Additionally, cisplatin, a chemotherapeutic agent derived from platinum salts, although not an herbal compound, is sometimes included in plant-based formulations. Cisplatin is known for its severe nephrotoxic effects, which occur when the drug accumulates in the kidneys and induces oxidative stress [26]. This leads to kidney injury, characterized by tubular damage, renal inflammation, and glomerular damage. Even when used in small doses in combination with herbal remedies, cisplatin can exacerbate renal damage, particularly in patients with pre-existing kidney conditions or those undergoing prolonged chemotherapy regimens [27]. Overall, while many bioactive compounds in herbal remedies provide substantial health benefits, their potential for causing hepatotoxicity and nephrotoxicity highlights the need for cautious use, particularly in individuals with pre-existing liver or kidney conditions.

Mechanisms of Toxicity in the Liver and Kidneys

The mechanisms underlying the hepatotoxicity and nephrotoxicity of bioactive compounds are complex and involve multiple pathways. One of the primary mechanisms is oxidative stress, which occurs when bioactive compounds generate reactive oxygen species (ROS) and reactive nitrogen species (RNS) [28]. These highly reactive molecules can overwhelm the body's natural antioxidant defenses, leading to cellular damage in both the liver and kidneys. ROS induce lipid peroxidation, which disrupts cellular membranes and impairs cellular functions [29]. In the liver, oxidative stress can result in the degeneration of hepatocytes (liver cells), leading to inflammation, fibrosis, and eventually cirrhosis [30]. Similarly, in the kidneys, oxidative

stress damages renal tubular cells, leading to tubular necrosis and interstitial fibrosis, contributing to kidney dysfunction [31]. Mitochondrial dysfunction is another key mechanism through which bioactive compounds induce toxicity in the liver and kidneys [32]. Mitochondria play a central role in cellular energy production and apoptosis regulation [33]. Many bioactive compounds interfere with mitochondrial function by impairing electron transport chain activity, leading to a decrease in ATP production [34]. This energy depletion makes the cells more vulnerable to damage and may lead to mitochondrial swelling, the release of pro-apoptotic factors like cytochrome c, and subsequent activation of caspases that drive programmed cell death (apoptosis) [34]. In both the liver and kidneys, mitochondrial dysfunction exacerbates oxidative stress, causing a vicious cycle of damage that ultimately leads to organ dysfunction.

In addition to oxidative stress and mitochondrial dysfunction, immune-mediated inflammation is a significant contributor to hepatotoxicity and nephrotoxicity [35]. Some bioactive compounds can activate immune cells, such as macrophages and T lymphocytes, triggering the release of pro-inflammatory cytokines like tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6) [36]. These cytokines promote inflammatory responses that can lead to tissue damage in the liver and kidneys [37]. Chronic inflammation can result in fibrosis, scarring, and the progressive loss of organ function. In the liver, this manifests as cirrhosis, and in the kidneys, it leads to the development of glomerulosclerosis and tubulointerstitial fibrosis [38,39]. Alteration of enzyme activity is another mechanism of toxicity. Many bioactive compounds in herbal remedies can modulate the activity of liver enzymes involved in the detoxification process, including cytochrome P450 enzymes [40]. These enzymes are responsible for metabolizing xenobiotics and other substances. However, when bioactive compounds interfere with their function, they can lead to the accumulation of toxic metabolites, further exacerbating liver and kidney damage. In some cases, bioactive compounds can inhibit these enzymes, leading to a reduced capacity to eliminate harmful substances from the body, thus contributing to organ toxicity [41]. In summary, the toxicity of bioactive compounds in the liver and kidneys is driven by a combination of oxidative stress, mitochondrial dysfunction, immune-mediated inflammation, and altered enzyme activity. These mechanisms can lead to cell death, fibrosis, and irreversible organ damage if the compounds are used

improperly or in excessive amounts. Understanding these pathways is critical for developing safer herbal remedies and ensuring that their therapeutic benefits outweigh the risks.

Risk Factors for Hepatotoxicity and Nephrotoxicity in Herbal Remedies

The use of bioactive compounds from herbal remedies can offer significant therapeutic benefits, but certain factors contribute to their potential hepatotoxicity (liver damage) and nephrotoxicity (kidney damage). These risk factors are essential for understanding and mitigating the adverse effects of herbal products. One of the primary risk factors for hepatotoxicity and nephrotoxicity associated with herbal remedies is excessive consumption or prolonged use of certain bioactive compounds. While many bioactive compounds exhibit therapeutic effects at lower doses, they can become toxic when taken in high quantities. Over time, high doses can overwhelm the body's detoxification capacity, leading to harmful accumulation of toxic metabolites in the liver and kidneys. For instance, compounds like pyrrolizidine alkaloids, found in several plants, may not produce noticeable toxicity at low doses but can lead to severe liver damage when consumed in high doses or over long periods [42]. Chronic exposure to such compounds can result in liver fibrosis, cirrhosis, and irreversible damage to renal tissues. Similarly, compounds such as aristolochic acid, found in *Aristolochia* species, can cause severe kidney damage when used excessively [23,24]. Prolonged use of herbal remedies without monitoring can lead to the accumulation of toxic compounds in the organs, causing irreversible harm [4].

Poor Standardization of Herbal Products

A significant risk factor for toxicity is the lack of standardization in the preparation of herbal products. Variability in the concentration of active compounds can lead to inconsistent therapeutic effects, and in some cases, unintentional toxicity [43]. Unlike pharmaceutical drugs, which undergo strict regulatory processes and quality control, herbal products are often produced without adequate oversight, leading to variations in potency [43]. These inconsistencies can be influenced by factors such as geographic location, harvest time, and the methods of extraction and formulation used [43]. For example, some herbal preparations may contain more of a particular bioactive compound than is intended, increasing the risk of side effects and toxicity [45]. This lack of standardization can lead to the development of adverse reactions in users, as some individuals may unknowingly be exposed to higher-than-expected doses of potentially toxic

compounds. The variation in quality and dosage makes it difficult to predict outcomes, contributing to an increased risk of harm, particularly to the liver and kidneys, which are responsible for detoxifying the body [46].

Pre-existing Liver or Kidney Conditions

Individuals with compromised liver or kidney function are more susceptible to the toxic effects of bioactive compounds. For example, patients with chronic liver disease or chronic kidney disease (CKD) may have reduced ability to metabolize and excrete herbal compounds, making them more vulnerable to toxicity [47]. These patients may experience more severe liver damage, kidney dysfunction, or even organ failure when exposed to certain bioactive compounds. Comorbidities such as diabetes and hypertension, which are common risk factors for liver and kidney disease, can further exacerbate the effects of bioactive compounds [48]. In diabetic patients, for example, the presence of diabetic nephropathy can amplify the nephrotoxic effects of herbal compounds like quercetin or silymarin, which may contribute to further kidney damage [49,50]. As a result, individuals with existing organ dysfunction should exercise caution when using herbal remedies and ideally consult a healthcare provider before starting such treatments.

Drug-Herb Interactions

Another critical risk factor for hepatotoxicity and nephrotoxicity is the potential interaction between bioactive compounds in herbal remedies and conventional pharmaceuticals. Many individuals with chronic conditions such as diabetes, hypertension, or cardiovascular disease often take multiple prescription medications [51]. Herbal remedies may interact with these medications, altering their pharmacokinetics (absorption, distribution, metabolism, and excretion), leading to either enhanced toxicity or reduced efficacy [52]. For instance, St. John's wort, a commonly used herbal remedy for depression, is known to induce the cytochrome P450 enzymes in the liver, which can accelerate the metabolism of drugs like warfarin, a blood thinner [53]. This interaction can result in reduced effectiveness of warfarin, increasing the risk of blood clotting. Conversely, certain herbal compounds may enhance the toxicity of medications. For example, compounds like kava (*Piper methysticum*) can increase the sedative effects of benzodiazepines, leading to excessive drowsiness or respiratory depression [54]. In the case of nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), combining these with herbal products that also exert renal stress can amplify kidney damage [55].

Recommendations for Safer Use of Bioactive Compounds

To reduce the risk of hepatotoxicity and nephrotoxicity associated with bioactive compounds, it is essential to adopt a more systematic and cautious approach to the use of herbal remedies. Several key measures can be taken to ensure the safe use of these compounds.

Standardization and Quality Control

A fundamental step toward ensuring the safety of herbal products is the implementation of rigorous standardization and quality control processes. Standardization would involve defining the exact concentrations of active ingredients in each dose of herbal remedies. This would help reduce variability in potency and minimize the risk of unintentional toxicity. Standardized products also enable healthcare providers to make more informed decisions when recommending herbal remedies as part of treatment regimens. Strict regulations for testing the quality and consistency of herbal products would be essential to ensuring their safety in clinical use.

Rigorous Toxicological Screening

Preclinical and clinical testing should be conducted on herbal remedies to evaluate their potential hepatotoxic and nephrotoxic effects. These studies should explore dose-response relationships and examine the long-term effects of bioactive compounds on liver and kidney function. Additionally, toxicological screenings should consider the interaction of herbal compounds with commonly used medications. Such screening would provide valuable data on the safety and efficacy of herbal remedies,

Bioactive compounds in herbal remedies offer numerous health benefits, particularly in the management of liver and kidney diseases. However, their safety must be carefully considered, especially when used in high doses or over extended periods. While many bioactive compounds provide protective effects against oxidative damage and inflammation,

allowing healthcare professionals to make evidence-based recommendations to patients.

Regulatory Oversight

Governments and health agencies should establish comprehensive regulatory frameworks to ensure the safety and efficacy of herbal products. This includes setting maximum allowable dosages, ensuring that herbal products are free from contaminants (such as heavy metals), and monitoring adverse events. Regulatory oversight would help minimize the risks of herbal remedies by ensuring that products sold to consumers are properly tested and labeled, allowing consumers to make safer choices.

Patient Education

Healthcare providers should prioritize patient education regarding the potential risks associated with herbal remedies. Educating patients on the importance of proper dosing, potential drug-herb interactions, and the risks of using herbal products in the presence of pre-existing liver or kidney conditions is critical. Patients should also be made aware of the importance of consulting with their healthcare provider before beginning any herbal treatment, especially if they are already on other medications. Education about the importance of using quality-controlled and standardized herbal products can also help prevent adverse reactions. In summary, to ensure the safe use of bioactive compounds, it is vital to focus on standardization, toxicological screening, regulatory oversight, and patient education. These measures will help mitigate the risks of hepatotoxicity and nephrotoxicity while enabling patients to benefit from the therapeutic effects of herbal remedies.

CONCLUSION

others may contribute to hepatotoxicity and nephrotoxicity when misused. To ensure the safe use of herbal remedies, it is critical to implement stringent regulatory frameworks, standardize formulations, and conduct thorough toxicological assessments.

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